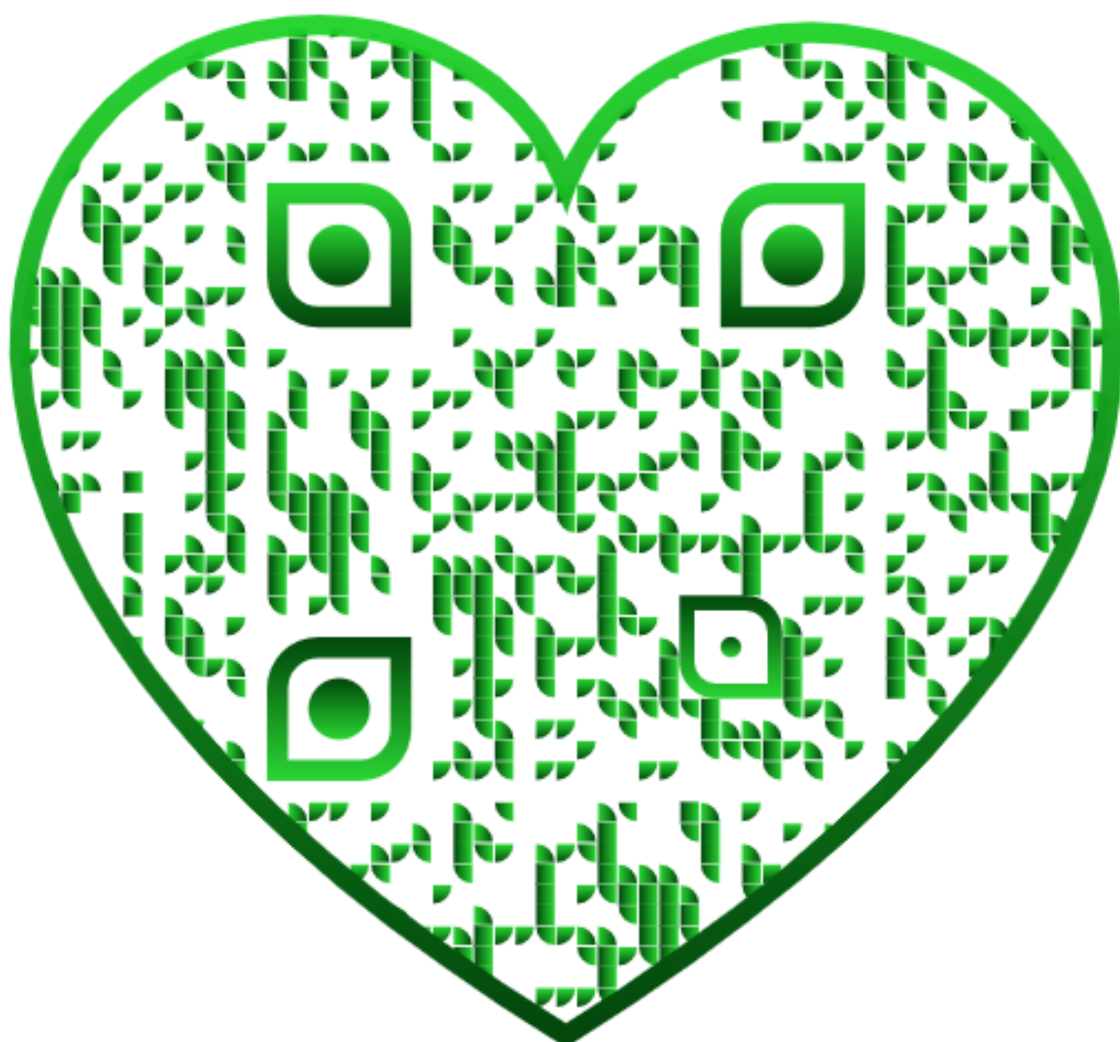


- ✓ Aminoglycoside-associated ATN is primarily due to accumulation of high drug concentrations within proximal tubular epithelial cells, and subsequent generation of **reactive oxygen species** that produce mitochondrial injury, which leads to cellular apoptosis and necrosis.
- ✓ Multiple risk factors for aminoglycoside-associated nephrotoxicity have been identified: the aggressiveness of aminoglycoside dosing, synergistic toxicity as the result of combination drug therapy, and preexisting clinical conditions of the patient.
- ✓ Aminoglycoside-associated ATN may be prevented by careful and cautious selection of patients and the use of alternative antibiotics whenever possible and as soon as microbial sensitivities are known. Commonly used alternatives include **fluoroquinolones** (eg, ciprofloxacin or levofloxacin) and **third- or fourth-generation cephalosporins** (eg, ceftazidime or cefepime). When aminoglycosides are necessary, **gentamicin**, **tobramycin**, and **amikacin** are most commonly used, but therapy should be selected to optimize antimicrobial efficacy. Furthermore, it is imperative to avoid volume depletion, limit the total aminoglycoside dose administered, and avoid concomitant therapy with other nephrotoxic drugs. *High-dose intermittent administration of aminoglycosides*, termed **once daily dosing**, used in combination with other antibiotics, has been intensively investigated as a practical cost-effective method to maintain antimicrobial efficacy while reducing the risk of AKI.
- ✓ Aminoglycoside use should be *discontinued or the dosage regimen revised* if AKI is evident. Other nephrotoxic drugs should be discontinued if possible, and the patient should be maintained adequately hydrated and hemodynamically stable. Short-term renal replacement therapy may be necessary.

2) Radiographic Contrast Media Nephrotoxicity

- ✓ Radiographic contrast media-induced AKI (CI-AKI) is the third leading cause of hospital-acquired AKI, accounting for 10% to 13% of cases.
- ✓ CI-AKI is usually transient in nature, presenting most commonly as nonoliguria with kidney injury apparent within **the first 24 to 48 hours** after the administration of contrast. The Scr concentration usually peaks between 3 and 4 days after exposure, with recovery after 7 to 10 days.
- ✓ The primary mechanisms by which contrast media induces nephrotoxicity are **renal ischemia** and **direct cellular toxicity**.
- ✓ Decreased renal blood flow exacerbates the ischemic and direct cytotoxic effects of contrast media on the renal tubules. Therefore, **preexisting kidney disease**, particularly in those with estimated GFR less than 60 mL/min/1.73 m², is the most important risk factor, since lower GFR is associated with increasing levels of risk. Other patient-specific risk factors



include conditions associated with decreased renal blood flow (ie, congestive heart failure, dehydration/volume depletion, and hypotension), and patients with atherosclerosis and reduced effective circulating arterial blood volume appear to also have an elevated risk. **Diabetes** is also a significant risk factor, likely due to coexisting kidney disease (diabetic nephropathy).

- ✓ Nephrotoxicity is best prevented in high-risk patients by using **alternative imaging procedures** (eg, ultrasound, noncontrast magnetic resonance imaging, and nuclear medicine scans). However, if contrast media must be used, the smallest adequate volume should be administered. If the ratio of the volume of contrast to be infused relative to the patient's creatinine clearance is greater than or equal to 3.7, the likelihood of nephrotoxicity is markedly increased. Therefore, in general, the volume of contrast administered should **not be greater than twice the baseline estimated creatinine clearance**. Low-osmolar nonionic (iohexol and iopamidol) and ionic (ioxaglate) contrast agents may be used to minimize the incidence of nephrotoxicity.
- ✓ There is no specific therapy available for managing established CI-AKI. Other nephrotoxic drugs should be discontinued if possible, and subsequent contrast studies must be appropriately timed to minimize cumulative toxicity. **Kidney function** (eg, Scr and urine output), electrolytes (eg, sodium and potassium), and volume status should be closely monitored.

3) Cisplatin Nephrotoxicity

- ✓ The primary dose-limiting toxicity of platin-containing compounds is nephrotoxicity. Cisplatin nephrotoxicity occurs in up to one-third of patients receiving the drug and is a significant cause of morbidity. **Carboplatin**, a 2nd-generation platinum analog, is associated with a lower incidence of nephrotoxicity than cisplatin and thus is the preferred agent in high-risk patients.
- ✓ Cisplatin administration results in impaired tubular reabsorption and decreased urinary concentration ability, leading to increased excretion of salt and water (ie, polyuria) within 24 hours of treatment.
- ✓ Cisplatin's nephrotoxicity is multifactorial in nature and likely begins with cellular uptake and accumulation of the drug in proximal tubular epithelial cells to concentrations that may reach five times the serum concentration.
- ✓ Risk factors include age more than 65 years, dehydration, preexisting kidney disease, renal irradiation, concurrent use of nephrotoxic drugs, large cumulative doses, and alcohol abuse.
- ✓ Renoprotective strategies include prospective dose reduction and decreased frequency of administration, which usually requires using the platin compounds in combination with other chemotherapeutic agents, avoiding concurrent use of other nephrotoxic drugs, and ensuring patients

are euvolemic or somewhat hypervolemic prior to initiating treatment. Vigorous hydration with isotonic saline should be used for all patients with a goal of maintaining at least 100 to 150 mL/hr of urine output during and after cisplatin treatment. **Amifostine**, an organic thiophosphate that is converted to an active metabolite, chelates cisplatin in normal cells and reduces the nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression associated with cisplatin and carboplatin therapy

- ✓ AKI caused by cisplatin therapy is usually partially reversible with time and supportive care, including dialysis. Kidney function indices should be closely followed, with Scr and BUN concentrations checked daily. Serum magnesium, potassium, and calcium concentrations should be monitored daily and corrected as needed.

4) Amphotericin B Nephrotoxicity

- ✓ Nephrotoxicity may be seen in nearly 30% of patients receiving median cumulative doses as low as 240 mg and reaches an incidence of greater than 80% when cumulative doses approach 5 g. Numerous studies demonstrate lower rates of nephrotoxicity with liposomal formulations compared with conventional amphotericin B.
- ✓ Dose-dependent nephrotoxicity is often evident after administration of cumulative doses of 2 to 3 g as nonoliguria, renal tubular potassium, sodium, and magnesium wasting, impaired urinary concentrating ability, and distal renal tubular acidosis.
- ✓ Amphotericin B nephrotoxicity occurs predominantly via two mechanisms. The first is direct tubular epithelial cell toxicity resulting from interaction of amphotericin B with ergosterol in the cell membrane, leading to increased tubular cell membrane permeability, lipid peroxidation, and eventual necrosis of proximal tubular cells. The second mechanism is afferent arteriolar vasoconstriction leading to a reduction in renal blood flow and GFR, and ischemic tubular injury.
- ✓ Risk factors that impact the likelihood of developing amphotericin B nephrotoxicity include preexisting kidney disease, large individual and cumulative doses, short infusion times, volume depletion, hypokalemia, increased age, and concomitant administration of diuretics and other nephrotoxins, including vancomycin and cyclosporine.
- ✓ Permanent decrements in GFR are best prevented by incorporating a low threshold (ie, if Scr reaches 2 mg/dL on 2 consecutive days) for stopping amphotericin B or switching to a liposomal formulation. Several lipid formulations of amphotericin B (eg, amphotericin B lipid complex, liposomal amphotericin B) are available and should be used in most high-risk patients as they reduce nephrotoxicity by enhancing drug delivery to sites of infection and reducing interaction with tubular epithelial cell membranes. Nephrotoxicity can also be minimized by limiting the

cumulative dose, increasing the infusion time, ensuring the patient is well hydrated, and avoiding concomitant administration of other nephrotoxins. Administration of 1 L IV 0.9% sodium chloride daily during the course of therapy reduces toxicity and a single infusion of saline 10 to 15 mL/kg prior to administration of each dose of amphotericin B is generally recommended. A number of other antifungal agents such as *itraconazole*, *voriconazole*, and *caspofungin* are viable alternatives and are now routinely used in lieu of amphotericin B for patients at high risk of developing nephrotoxicity. Administration of the antioxidant N-acetylcysteine (600 mg orally twice daily in adults) during amphotericin treatment may be nephroprotective.

5) Osmotic Nephropathy

- ✓ Several drugs, including mannitol, low-molecular-weight dextran, hydroxyethyl starch, and radiographic contrast media, or drug vehicles, such as sucrose, maltose, and propylene glycol, are associated with osmotic nephropathy, which may rarely lead to ATN and AKI
- ✓ **The clinical presentation** of osmotic nephropathy is often subtle. While tubular proteinuria or vacuolated tubular cells may be observed on urinalysis for patients with AKI, the definitive diagnosis of osmotic nephropathy is only made via a kidney biopsy.
- ✓ **Risk factors** for osmotic nephropathy include excessive doses of offending agents, preexisting kidney disease, ischemia, older age (greater than 65 years), and concomitant use of other nephrotoxins. Nephrotoxicity may be prevented by limiting the dose, reducing the rate of infusion, and avoiding dehydration and concomitant nephrotoxins

✗ Hemodynamically Mediated Kidney Injury

- ✓ Hemodynamically mediated kidney injury generally refers to any cause of AKI resulting from an acute decrease in intraglomerular pressure, including “prerenal” states leading to reduced effective renal blood flow (eg, hypovolemia and congestive heart failure) and medications that affect the renin–angiotensin system (RAS). Within each nephron, blood flow and pressure are regulated by glomerular afferent and efferent arterioles to maintain intraglomerular capillary hydrostatic pressure, glomerular filtration, and urine output. **Afferent** and **efferent** arteriolar vasoconstrictions are primarily mediated by angiotensin II, whereas afferent vasodilation is primarily mediated by prostaglandins. Drug-induced causes of hemodynamic kidney injury typically stem from constriction of glomerular afferent arterioles and/or dilation of glomerular efferent arterioles. ACEIs, angiotensin II receptor blockers (ARBs), and NSAIDs are the agents that have been most commonly implicated.

1) ACEis and ARBs

- ✓ Patients with renal artery stenosis, volume depletion, and congestive heart failure and those with preexisting kidney disease, including diabetic nephropathy, are most likely to experience a significant decline in kidney function when therapy with one of these agents is initiated
- ✓ An increase in Scr of up to 30% is commonly observed within 3 to 5 days of initiating therapy and is an indication that the drug has begun to exert its desired pharmacologic effect. The increase in Scr typically stabilizes within 1 to 2 weeks and is usually reversible upon stopping the drug.
- ✓ ACEIs—or ARB-mediated kidney injury—is primarily the result of disruption of normal autoregulation of intraglomerular capillary hydrostatic pressure. When ACEI or ARB therapy (eg, enalapril or candesartan) is initiated, the synthesis of angiotensin II is decreased, or blocked, respectively, thereby preferentially dilating the efferent arteriole.
- ✓ **Risk factors** include patients with bilateral renal artery stenosis or stenosis in a single kidney (ie, renal transplant); patients with decreased effective arterial blood volume (ie, prerenal states), especially those with decompensated congestive heart failure, volume depletion from excess diuresis or GI fluid loss, hepatic cirrhosis with ascites, and nephrotic syndrome; patients with preexisting kidney disease; and patients receiving concurrent nephrotoxic drugs, particularly other drugs that affect intraglomerular autoregulation such as NSAIDs.
- ✓ A common strategy for at-risk patients is to initiate therapy with low doses of a short-acting ACEI (eg, captopril 6.25-12.5 mg), then gradually titrate the dose upward, and convert to a longer-acting agent after patient tolerance has been demonstrated. Outpatients may be started on low doses of long-acting ACEIs (eg, enalapril 2.5 mg) with gradual dose titration every 2 to 4 weeks until the maximum dose or desired response is achieved. Kidney function indices and serum potassium concentrations must be monitored carefully, daily for hospitalized patients and every 2 to 3 days for outpatients.
- ✓ Acute decreases in kidney function and the development of hyperkalemia usually resolve over several days after ACEI or ARB therapy is discontinued. ACEIs or ARB therapy may frequently be reinitiated, particularly for patients with congestive heart failure, after intravascular volume depletion has been corrected or diuretic doses reduced. Slight reductions in kidney function (maintenance of a Scr concentration of 2-3 mg/dL) may be an acceptable trade-off for hemodynamic improvement in certain patients with severe congestive heart failure or renovascular disease not amenable to revascularization.

2) NSAIDs and COX-2 Inhibitors

- ✓ NSAID- and COX-2-induced AKI usually occurs within 2 to 7 days of initiating therapy, particularly with a short-acting agent such as ibuprofen, or within days of some other precipitating event (eg, intravascular volume depletion). Patients typically present with complaints of diminished urine output, weight gain, and/or edema. Urine sodium concentrations (less than 20 mEq/L) and fractional excretion of sodium (less than 1%) are usually low, and BUN, Scr, potassium, and blood pressure are typically elevated. The urine sediment is usually bland and unchanged from baseline but may show occasional RTECs and granular casts.
- ✓ The pathogenesis of NSAID- and COX-2-induced AKI lies in the disruption of normal intraglomerular autoregulation.
- ✓ **Risk factors** for NSAID- and COX-2-induced AKI include age more than 60 years, preexisting kidney disease, hepatic disease with ascites, congestive heart failure, intravascular volume depletion/dehydration, systemic lupus erythematosus, or concurrent treatment with diuretics, ACEIs, or ARBs.
- ✓ NSAID- and COX-2 inhibitor-induced AKI can be prevented by recognizing high-risk patients, avoiding potent compounds such as **indomethacin** and using analgesics with less prostaglandin inhibition, such as acetaminophen, nonacetylated salicylates, aspirin, and possibly nabumetone. When NSAID therapy is essential for high-risk patients, the *minimal effective dose* should be used for the *shortest duration possible*, and NSAIDs with **short half-lives** should be considered (eg, sulindac) along with optimal management of predisposing medical problems and frequent kidney function monitoring. Moreover, use of concurrent hypotensive agents and other drugs that affect renal hemodynamics (eg, ACEIs, ARBs, diuretics) should be discouraged in high-risk patients and dehydration avoided.
- ✓ NSAID-induced AKI is treated by discontinuation of therapy and supportive care. Use of other nephrotoxic drugs should be avoided. Kidney injury is rarely severe, and kidney function generally recovers within 3 to 5 days.

3) Cyclosporine and Tacrolimus

- ✓ Nephrotoxicity remains a major dose-limiting adverse effect of both drugs. The reversible AKI occurred frequently in transplant recipients during the first 6 months of cyclosporine therapy
- ✓ The acute hemodynamic changes associated with calcineurin inhibitor nephrotoxicity result from an increase in potent vasoconstrictors including thromboxane A₂ and endothelin, activation of the RAS and sympathetic nervous systems, as well as a reduction in the vasodilators nitric oxide, prostacyclin, and prostaglandin E₂.

- ✓ **Risk factors** include age over 65, higher dose, concomitant therapy with nephrotoxic drugs (particularly NSAIDs), and interacting drugs that inhibit calcineurin inhibitor metabolism and transport and thus increase systemic exposure, older kidney allograft age, salt depletion, diuretic use, and polymorphic expression of P-glycoprotein.
- ✓ Pharmacokinetic and pharmacodynamic monitoring is an important means of preventing toxicity. Decreased doses of cyclosporine or tacrolimus, primarily when used in combination with other nonnephrotoxic immunosuppressants, may minimize the risk of toxicity, but this may increase the risk of chronic rejection.
- ✓ AKI usually improves with dose reduction and treatment of contributing illness or the discontinuation of interacting drugs. CKD is usually irreversible, but progressive toxicity may be limited by discontinuation of cyclosporine (or tacrolimus) therapy or dose reduction, with the continuation of other immunosuppressant.

✎ Obstructive Nephropathy

- ✓ Numerous medications may cause obstructive nephropathy, or kidney injury from deposition or precipitation within the renal tubules and/or collecting system. For example, the precipitation of drug crystals in distal tubular lumens can lead to intratubular obstruction, interstitial nephritis, and occasionally superimposed ATN, collectively termed "crystal nephropathy." *Nephrolithiasis*, the formation of stones within the kidney, results from abnormal crystal precipitation in the renal collecting system, potentially causing urinary tract obstruction with kidney injury

1) Crystal Nephropathy

- ✓ Drugs may induce intratubular obstruction and AKI by *direct* (precipitation of the drug itself) and *indirect* means (ie, promoting release and precipitation of tissue-degradation products or cellular casts). For example, antineoplastic drugs may cause acute renal tubular obstruction indirectly by inducing tumor lysis syndrome, hyperuricemia, and intratubular precipitation of uric acid crystals.
- ✓ Uric acid precipitation can be prevented by *vigorous hydration with normal saline*, beginning at least 48 hours prior to chemotherapy, to maintain urine output 100 mL/hr in adults. Administration of *allopurinol* 100 mg/m² thrice daily (maximum of 800 mg/day) started 2 to 3 days prior to chemotherapy, and *urinary alkalinization* to pH 7 may also be of value.

2) Vancomycin Cast Nephropathy

- ✓ Vancomycin-associated AKI may also be due to the formation of obstructive tubular casts composed of noncrystal nanospheric vancomycin aggregates admixed with uromodulin. These distinctive casts are observed in some patients with AKI associated with high vancomycin trough concentrations. On kidney biopsy, acute tubulointerstitial

inflammation is associated with these tubular casts. Co-precipitation of vancomycin and uromodulin occurs

3) Nephrolithiasis

- ✓ Drug-induced nephrolithiasis can be the result of abnormal crystal precipitation in the renal collecting system, potentially causing pain, hematuria, infection, or, occasionally, urinary tract obstruction with kidney injury. The overall prevalence of drug-induced nephrolithiasis is about 1% to 2% of all cases of nephrolithiasis.
- ✓ **Triamterene** had been the drug most frequently associated with kidney stone formation, with a prevalence of 0.4%. **Sulfadiazine** is a poorly soluble sulfonamide that may cause symptomatic acetylsulfadiazine crystalluria with stone formation and flank or back pain, hematuria, or kidney injury. A high urine volume and urinary alkalinization to pH greater than 7.15 may be protective.

Glomerular disease

- ✓ Proteinuria, particularly nephrotic range proteinuria (defined as urine protein excretion greater than 3.5 g/day) with or without a decline in the GFR is a hallmark sign of glomerular injury.
- ✓ Glomerular injury associated with drug exposure is broadly classified into either **direct cellular toxicity** or **immune-mediated injury**. Glomerular lesions associated with direct cellular toxicity include thrombotic microangiopathy, minimal change glomerular disease, and focal segmental glomerulosclerosis (FSGS). Lesions from immune-mediated injury include vasculitis and membranous nephropathy.

1) Minimal change disease

- ✓ Drug-induced minimal change glomerular disease is frequently accompanied by interstitial nephritis and is most common during NSAID therapy. Lithium, pamidronate, interferon- α , and interferon- β have also been implicated.
- ✓ Patients present abruptly with nephrotic range proteinuria, hypoalbuminemia, and hyperlipidemia and rarely with hematuria and hypertension.
- ✓ Proteinuria usually resolves rapidly after discontinuation of the offending drug, and a course of corticosteroids (eg, prednisone) may help resolve the lesion.

2) Focal Segmental Glomerulosclerosis

- ✓ FSGS is characterized by patchy areas (ie, only some glomeruli are partially affected by the disease) of glomerular sclerosis with interstitial inflammation and fibrosis
- ✓ It represents a pattern of glomerular injury, not a disease per se, and is the final common pathway by which normal glomerular components are replaced by fibrous scar tissue.

- ✓ Patients receiving IV formulations, high doses, or prolonged therapy are at highest risk. Interferon- α , interferon- β , lithium, sirolimus, and anabolic steroids have also been associated with FSGS.

3) Membranous Nephropathy

- ✓ It is characterized by subepithelial immune complex formation along glomerular capillary loops and, although rarely seen, has classically been associated with gold therapy, penicillamine, captopril, and NSAID use.
- ✓ Proteinuria usually resolves slowly after discontinuing the offending drug. Patients who remain nephrotic after 6 months should be treated with a 6- to 12-month course of immunosuppressive therapy, which typically consists of prednisone with or without cyclophosphamide.

3.4. Chronic Kidney Disease (CKD)

✍ Definition

- Kidney damage for more than 3 months, as defined by structural or functional abnormality of the kidney, manifested by either pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities in imaging tests¹. Functional abnormalities are indicated by a decline in glomerular filtration rate (GFR) less than 60 mL/min/1.73m² (0.58 mL/s/m²).
- GFR <90 mL/minute/1.73m² for >3 months, with or without kidney damage
- CKD is categorized by the level of kidney function (as defined by GFR) into stages 0 through 5, with each increasing number indicating a more advanced stage of the disease

✍ Classification of Chronic Kidney Disease

- Normal kidney function in adults is about 120 mL/min/1.73 m² of GFR.
- Even though a GFR of >90 mL/min/1.73 m² is considered normal kidney function, a patient can be diagnosed with CKD if the patient has proteinuria, hematuria, or evidence of structural damage from a kidney biopsy. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA. Stage G5 CKD is referred to as end-stage renal disease (ESRD) or end-stage kidney disease.

¹ Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, Griffith KE, Hemmelgarn BR, Iseki K, Lamb EJ: **Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.** *Kidney international supplements* 2013, 3(1):1-150.

Table 3.1 KDIGO GFR and albuminuria categories and prognosis of CKD by category¹

				Persistent albuminuria		
				A1	A2	A3
				Normal to mildly increase <30mg/g	Moderately increased 30 -300 mg/g	Severely increased >300 mg/g
GFR categories (mL/min/1.73m ²)	G1	Normal or high	≥90			
	G2	Mildly decreases	60 – 89			
	G3a	Mild to moderate	45 – 59			
	G3b	Moderate to severe	30 – 44			
	G4	Severely decreased	15 – 29			
	G5	Kidney failure	< 15			
Low risk				High risk		
Moderately increased risk				Very high risk		

Etiology

1. Susceptibility Factors

- ✓ Associated with an **increased risk**, but not proven to directly cause CKD
- ✓ Mostly **not modifiable**

- ↳ Advanced age
- ↳ Low income or education
- ↳ Racial/ethnic minority
- ↳ Reduced kidney mass
- ↳ Low birth weight
- ↳ Family history of CKD
- ↳ Systemic inflammation
- ↳ Dyslipidemia

2. Initiation Factors

- ✓ Initiation factors are conditions that directly **result in kidney damage**
- ✓ **Modifiable** by pharmacologic therapy.

¹ Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, Griffith KE, Hemmelgarn BR, Iseki K, Lamb EJ: **Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.** *Kidney international supplements* 2013, 3(1):1-150.

- ✚ Diabetes mellitus
- ✚ Hypertension
- ✚ Autoimmune diseases
- ✚ Polycystic kidney disease
- ✚ Systemic infections
- ✚ Urinary tract infections
- ✚ Urinary stones
- ✚ Lower urinary tract obstructions, and
- ✚ Drug toxicity

3. Progression Factors

- ✓ Progression risk factors are those associated with **further kidney damage**.
- ✓ The most important predictors of progressive CKD
 - ✚ Proteinuria
 - ✚ Elevated blood pressure
 - ✚ Hyperglycemia
 - ✚ Hyperlipidemia, and
 - ✚ Smoking.

✚ Pathophysiology

- Damage to the kidney results from any of the *initiation factors* which resulting in *loss of nephron mass*. The resultant effect is *hypertrophy of the remaining nephrons* to compensate for the loss of renal function and nephron mass. These adaptive changes result in an *increase in glomerular filtration and tubular function*, both reabsorption and secretion, in the remaining nephrons. As time progresses, *glomerular capillary pressure is increased*, mediated by *angiotensin II*, to maintain the hyper filtration state of the functioning nephrons. Increased glomerular capillary pressure *expands the pores* in the glomerular basement membrane, altering the size-selective barrier and allowing *proteins* to be filtered through the glomerulus. Filtered proteins are *reabsorbed* in the renal tubules, which activates the tubular cells to produce *inflammatory and vasoactive cytokines* and *triggers complement activation*. These in turn cause interstitial damage and scarring within the renal tubules, leading to damage and *loss of more nephrons*.

✚ Clinical Presentation

- Symptoms
 - ✓ Stages 1 and 2 CKD are generally asymptomatic.
 - ✓ Stages 3 and 4 CKD may be associated with minimal symptoms.
 - ✓ Typical symptoms associated with stage 5 CKD include pruritus, dysgeusia, nausea, vomiting, constipation, muscle pain, fatigue, and bleeding abnormalities.
- Signs
 - ✓ CV: worsening HTN, edema, dyslipidemia, left ventricular hypertrophy, electrocardiographic changes and chronic heart failure.
 - ✓ Genitourinary: changes in urine volume and consistency, "foaming" of urine (indicative of proteinuria), and sexual dysfunction.

✚ Laboratory Tests for CKD

- I. Increased BUN and SCr and decreased GFR

2. Increased K, P, and Mg; ↓bicarbonate (metabolic acidosis); calcium levels are generally low in earlier stages of CKD and may be elevated in stage 5 CKD, 2^o to the use of Ca-containing phosphate binders.
3. Decreased albumin, if inadequate nutrition intake in advanced stages.
4. Decreased RBC count, Hgb and Hct
5. Proteinuria or albuminuria: urine positive for albumin or protein
 - ✓ Normal: <30mg/24hrs
 - ✓ Microalbuminuria: 30-300mg/24hrs
 - ✓ Macroalbuminuria (overt proteinuria): >300mg/24hrs
 - ✓ Nephrotic range proteinuria: >3g/24hrs.
6. Increased parathyroid hormone (PTH) level
7. Decreased vitamin D levels (stages 4 or 5 CKD).

✎ Treatment of CKD

- Desired Outcomes
 - ✓ The primary goal is to slow and prevent the progression of CKD
- Nonpharmacologic Therapy
 - ✓ Dietary Protein Restriction:
 - ✎ Shown to slow the progression of kidney disease. However, protein restriction must be balanced with the risk of malnutrition in patients with CKD. Patients with a GFR less than 25mL/minute/1.73m² received the most benefit from protein restriction; therefore, patients with a GFR above this level should not restrict protein intake. Patients who have GFR <25mL/min/1.73m² who are not receiving dialysis should restrict protein intake to **0.6 g/kg** per day.
 - ✎ Malnutrition is common in patients with ESRD due to decreased appetite, hypercatabolism, nutrient losses through dialysis. For this reason, patients receiving dialysis should maintain protein intake of **1.2 – 1.3 g/kg** per day
- Pharmacologic Therapy
 1. **Intensive Blood Glucose Control:**
 - ✓ Intensive insulin therapy to maintain preprandial blood glucose levels between 70 and 125 g/dL and postprandial blood glucose levels less than 180 g/dL
 2. **Optimal Blood Pressure Control:**
 - ✓ Stages 1-4: goal BP of less than 130/80 mm Hg
 - ✓ Stage 5: receiving hemodialysis, goal BP of <140/90 mm Hg before hemodialysis and <130/80 after hemodialysis.
 3. **Reduction in Proteinuria**
 - ✓ ACE inhibitors and ARBs:
 - ✎ Decrease glomerular capillary pressure and volume because of their effects on angiotensin II.
 - ✎ This, in turn, reduces the amount of protein filtered through the glomerulus, independent of the reduction in blood pressure

↪ Antihypertensive agents of choice for all patients with CKD.

4. Hyperlipidemia Treatment

- ✓ CKD patients are among the highest-risk group for cardiovascular conditions (i.e., equivalent to that of patients with known coronary heart disease)
- ✓ Should be treated aggressively for dyslipidemia to an LDL cholesterol goal below 100 mg/dL

✎ Complications of CKD

1. Fluid and Electrolyte Abnormalities

a) Impaired Sodium and Water Homeostasis

- ✓ Sodium and water balance are primarily regulated by the kidney.
- ✓ Reductions in nephron mass ↓GF → reabsorption of Na and water → edema.
- ✓ Treatment

↪ **Nonpharmacologic:** Sodium and fluid restrictions

↪ **Pharmacologic:** Loop diuretics therapy

b) Impaired Potassium Homeostasis

- ✓ Potassium balance is primarily regulated by the kidney via the distal tubular cells. Reduction in nephron mass decreases tubular secretion of potassium, leading to **hyperkalemia**.
- ✓ Nonpharmacologic treatment: avoid abrupt increases in dietary intake of potassium, dialysis
- ✓ Pharmacologic

↪ Patients who present with **cardiac abnormalities** caused by hyperkalemia should receive **calcium gluconate or chloride** (1 g IV) to reverse the cardiac effects

↪ Temporary measures can be employed to shift extracellular potassium into the intracellular compartment to stabilize cellular membrane effects of excessive serum potassium levels. The use of **regular insulin** (5 to 10 units IV) and **dextrose** (5% to 50% IV), or nebulized **albuterol** (10 to 20 mg). These measures will decrease serum potassium levels within 30 to 60 minutes after treatment, but potassium must still be removed from the body. Shifting potassium to the intracellular compartment, however, decreases potassium removal by dialysis. Often, **multiple dialysis sessions** are required to remove potassium that is redistributed from the intracellular space back into the serum.

↪ **Sodium polystyrene sulfonate** (SPS, 15 to 30 g orally), a Na-K exchange resin, promotes potassium excretion from the GI tract

2. Metabolic Acidosis

- ✓ Normal metabolism of ingested food produces approximately 1 mEq/kg of metabolic acid daily, which must be excreted by the kidneys (primarily as ammonium ion) to maintain acid-base balance. Reduced bicarbonate

reabsorption and impaired production of ammonia by the kidneys are the major factors responsible for development of metabolic acidosis in advanced kidney disease. Can be treated with Na bicarbonate, or dialysis.

3. Anemia of CKD

- ✓ The progenitor cells of the kidney produce 90% of the hormone **erythropoietin (EPO)**, which stimulates RBC production.
- ✓ Reduction in nephron mass → decreases renal production of EPO → anemia in patients with CKD.
- ✓ Anemia of CKD → decreased oxygen delivery and utilization, → increased cardiac output and left ventricular hypertrophy (LVH) → the cardiovascular risk and mortality in patients with CKD. The result is a *normochromic, normocytic anemia*.
- ✓ Uremia decreases the lifespan of RBCs from a normal of **120** days to as low as **60** days in patients with stage 5 CKD.
- ✓ Iron deficiency and *blood loss from regular laboratory testing and hemodialysis* also contribute to the development of anemia in patients with CKD
- ✓ Treatment

➤ The goal of treatment for anemia of CKD is to increase Hgb levels greater than **11 g/dL**

➤ **Nonpharmacologic Therapy:**

1. Sufficient dietary iron intake must be maintained in patients with anemia of CKD. Approximately **1 to 2mg** of iron is absorbed daily from the diet. This small amount is generally not adequate to preserve adequate iron stores to promote RBC production.
2. RBC transfusions

➤ **Pharmacologic Therapy**

1. **Iron supplementation** to correct and prevent iron deficiency caused by ongoing blood loss and increased iron demands associated with the initiation of erythropoietic therapy
2. **ESA** to correct erythropoietin deficiency: *epoetin alfa, epoetin beta and darbepoetin alfa*. The first-line treatment for anemia of CKD involves replacement of erythropoietin with ESAs. Darbepoetin alfa differs from epoetin alfa by the addition of carbohydrate side chains that increase the half-life of darbepoetin alfa compared to epoetin alfa and endogenous EPO, allowing for less frequent dosing than that of epoetin alfa. The most common adverse effect seen with ESA is increased BP. The starting doses of epoetin alfa are **80 to 120 units/kg** per week for SC administration and **120 to 180 units/kg** per week for IV administration, divided two to three times per week. The starting dose of darbepoetin alfa is **0.45 mcg/kg**, SC or IV once weekly

4. Secondary Hyperparathyroidism and Renal Osteodystrophy

- ✓ As renal function declines in patients with CKD, decreased phosphorus excretion disrupts the balance of calcium and phosphorus homeostasis.
- ✓ The rise in serum phosphate causes increased binding of phosphate with calcium in the plasma, thus decreasing the plasma serum ionized calcium concentration
- ✓ The parathyroid glands release PTH in response to decreased serum ionized calcium and increased serum phosphorus levels. The actions of PTH include increasing calcium resorption from bone, increasing calcium reabsorption from the proximal tubules, decreasing phosphorus reabsorption in the proximal tubules, stimulating activation of vit D by 1- α -hydroxylase to calcitriol (1,25-dihydroxyvitamin D₃) to promote calcium absorption in the GI tract and increased calcium mobilization from bone. The actions of calcitriol (the active form of vitamin D), increases gut absorption of calcium and suppress PTH release (negative feedback). As kidney function continues to decline and the GFR falls < 60, phosphorus excretion continues to ↓ (hyperphosphatemia) and calcitriol production ↓ es that finally leads to secondary hyperparathyroidism (sHPT).

✓ Treatment

✚ Nonpharmacologic Therapy

- ❖ Dietary phosphorus restriction
- ❖ Restriction of aluminum exposure and
- ❖ Parathyroidectomy.

✚ Pharmacologic Therapy

1. **Phosphate-Binding Agents:** Used to bind dietary phosphate in the GI tract to form an insoluble complex that is excreted in the feces
 - i. Calcium-based phosphate binders:
 - Calcium carbonate (40% elemental Ca) and calcium acetate (25% elemental Ca)
 - Starting Dose 0.5–1g elemental Ca 3x/day
 - Adverse effects: constipation and hypercalcemia
 - ii. Aluminum/magnesium-based phosphate binders:
 - Aluminum hydroxide, aluminum carbonate, Magnesium hydroxide, magnesium carbonate
 - Not recommended for chronic use
 - iii. Lanthanum carbonate: Quickly dissociates in the acidic environment of the stomach, where the lanthanum ion binds to dietary phosphorus, forming an insoluble compound that is excreted in the feces
2. **Vitamin D (calcitriol)**
 - ❖ Vitamin D occurs naturally as **ergocalciferol** (vitamin D₂) and **cholecalciferol** (vitamin D₃), both of which are inactive precursors of active forms of vitamin D.

- ❖ An intermediate activation step (25-hydroxylation) occurs in the liver to produce 25-hydroxy vitamin D (25-hydroxycalciferol), which is also relatively inactive. Final activation (1-hydroxylation) occurs in the kidney, yielding calcitriol (1,25-dihydroxycholecalciferol), the active form of vit D. Exogenous vitamin D compounds that mimic the activity of calcitriol decrease PTH secretion. (**calcitriol, paricalcitol, doxercalciferol, alfacalcidol**)
- ❖ Dosing: usually **0.25–0.5 mcg/day**

3.5. Glomerulonephritis

✎ Introduction

- The glomerulus consists of two important components:
 1. Filtration barrier (capillary wall): Consists of 3 well-defined layers: fenestrated endothelium, glomerular basement membrane (GBM), and epithelial cell layer (podocytes)
 2. Mesangium: provides support for the glomerular capillaries
- The passage of solutes through the glomerular membrane is impacted by both the **size** and **charge** of the solute.
- The unique capillary bed of the glomerulus;
 - ✓ Allows free passage of small nonprotein plasma constituents up to the size of inulin (MW of 5.2 kDa) whereas it excludes macromolecules $\geq$ albumin (MW of 69 kDa). Fixed, negatively charged sites are found within the glomeruli in all three layers of the capillary wall. The movement of negatively charged molecules is thus restricted more than that of neutral or positively charged molecules. Different glomerular diseases affect this size - and charge-selective barrier to different extents

✎ Pathogenesis

- Genetic mutations producing familial disease
- Systemic hypertension and atherosclerosis can produce pressure stress, ischemia, or lipid oxidants that lead to chronic glomerulosclerosis
- Diabetic nephropathy: thickening of the GBM secondary to the long-standing effects of hyperglycemia, advanced glycosylation end products, and reactive oxygen species.
- Infections: Bacteria, fungi, and viruses can directly infect the kidney producing their own antigens.
- Poststreptococcal glomerulonephritis
- Autoimmune diseases

✎ Clinical Presentation

- Patients with glomerular disease are often categorized into one of two broad classifications:
 - ✓ Nephritic syndrome: reflects glomerular inflammation → **hematuria**

- ✓ Nephrotic syndrome: noninflammatory injury to the glomerular structures and results in few cells or cellular casts in the urine

1) Nephritic Syndrome

- ✓ Acute nephritic syndromes classically present with hypertension, hematuria, RBC casts, pyuria, and mild to moderate proteinuria.
- ✓ Extensive inflammatory damage to glomeruli causes a fall in GFR and eventually produces uremic symptoms with salt and water retention, leading to edema and hypertension

- ✓ Causes:

- ✚ **Poststreptococcal Glomerulonephritis:** Affects children between the ages of 2 and 14 years. Skin (impetigo) and throat infections (pharyngitis) with particular M types of streptococci (nephritogenic strains) antedate glomerular disease. PSGN due to impetigo develops 2–6 weeks after skin infection and 1–3 weeks after streptococcal pharyngitis. Treatment is supportive, with control of hypertension, edema, and dialysis as needed. Antibiotic treatment for streptococcal infection should be given to all patients and their cohabitants

- ✚ **Other causes:** subacute bacterial endocarditis, lupus nephritis, antiglomerular basement membrane disease, IgA nephropathy

2) Nephrotic Syndrome

- ✓ Nephrotic syndrome classically presents with

- ✚ Heavy proteinuria (>3.5 g/day per 1.73 m²): urine dipstick 3+/4+
- ✚ Hypoalbuminemia, <2.5 g/dL
- ✚ Hypercholesterolemia, >200 mg/dL
- ✚ Edema, and Hypertension
- ✚ Hypercoagulable state

- ✓ Causes

- ✚ Minimal change disease: alters capillary charge and podocyte integrity, **the most common form of nephrotic syndrome**
- ✚ Focal segmental glomerulosclerosis
- ✚ Membranous glomerulonephritis: CA (solid tumors of the breast, lung, colon), infection (hepatitis B, malaria, schistosomiasis), or rheumatologic disorders like lupus or rarely rheumatoid arthritis
- ✚ Diabetic nephropathy

✚ Diagnosis

- Laboratory evaluation

1) Urinalysis: to determine nephrotic nature of glomerular disease

- ✦ Proteinuria, >3.5 g/day/ 1.73 m²
- ✦ Lipiduria

- ✚ To determine nephritic nature of glomerular disease: hematuria, pyuria cellular, granular casts

2) Glomerular filtration rate: to determine extent of glomerular damage

- 3) **Percutaneous renal biopsy:** to provide definitive diagnosis of glomerular disease
- 4) **Other tests:** to identify type and etiology of glomerular disease
 - ❖ Serum complement concentration
 - ❖ Antinuclear and anti-DNA antibodies
 - ❖ Antistreptolysin antibodies
 - ❖ Circulating antiglomerular basement membrane antibodies
 - ❖ Cryoglobulins

Treatment

- Supportive Therapy

- 1) For edema:
 - ↳ Salt restriction, bedrest, and use of support stockings
 - ↳ Diuretics - Furosemide: 160 to 480 mg
 - 2) Hypertension: < 130/80 mm Hg
 - ↳ ACEI/ARBs
 - ↳ CCB (nondihydropyridines)
 - 3) Proteinuria: Dietary protein restriction, ACEI/ARB
 - 4) Hyperlipidemia: A low-fat diet, Statins (lovastatin, pravastatin, simvastatin, and fluvastatin)
 - 5) Anticoagulation: Warfarin
 - ❖ Patients who have documented thromboembolic episodes
 - ❖ Albumin < 2.0 to 2.5 g/dL
- **Corticosteroids for the management of minimal change nephrotic syndrome (MCNS)**
 - ✓ Initial dose of 60 mg/m² per day (2 mg/kg per day), with a maximum dose of 60 mg/d administered for 4 to 6 weeks. This is then followed by a dose of 40 mg/m² per dose (1.5 mg/kg) every other day for 2 to 5 months, with tapering of the dose.
 - ✓ Common definitions of patients with nephrotic syndrome related to steroid treatment outcome
 - ↳ **Remission:** urine protein: creatinine ratio <0.2 or dipstick negative or trace reading for 3 consecutive days
 - ↳ **Relapse:** increase in first morning urine protein: creatinine ratio to ≥2 or dipstick reading of ≥2+ for 3 of 5 consecutive days
 - ↳ **Corticosteroid responsive:** attainment of complete remission with corticosteroid therapy
 - ↳ **Corticosteroid resistance:** inability to induce a remission within 4 weeks of daily corticosteroid therapy
 - ↳ **Infrequent relapse:** 1–3 relapses annually
 - ↳ **Frequent relapse:** ≥2 relapses within 6 months after initial therapy or ≥4 relapses in any 12-month period

✎ **Corticosteroid dependent:** relapse during taper or within 2 weeks of discontinuation of corticosteroid therapy

- ✓ Patients who *relapse* are treated with another course of prednisone with the goal of decreasing the chance of corticosteroid toxicity by weaning soon after the patient is in remission.

✎ 60 mg/m² per day of corticosteroids as with initial presentation with weaning to alternate-day therapy (40 mg/m² per dose) after a urine dipstick test result is negative or trace for protein for 3 consecutive days

- Infrequent relapsers: 4-week alternate-day therapy
- Frequent relapse: 3-month alternate-day therapy

- ✓ Corticosteroid resistant MCNS: cyclophosphamide, levamisole, cyclosporine

✎ Evaluation of Therapeutic Outcomes

- For therapeutic response and treatment-related toxicities
- ✓ Serum creatinine concentration and creatinine clearance
- ✓ Blood pressure should be monitored periodically
- ✓ Serum lipid concentrations
- ✓ Urinalysis and a complete blood count
- ✓ Patient's appetite and energy level

3.6. Electrolyte Disorders

✎ Introduction

- Electrolytes are involved in numerous metabolic and homeostatic processes throughout the body. Abnormalities are associated with excessive or reduced intake, altered absorption and excretion, or changes in hormonal and neurological homeostasis
- Normal electrolyte serum concentrations Na: 135 – 145 mEq/L, K: 3.5 – 5.0 mEq/L, Mg: 1.4 – 1.8 mEq/L, Ca: 8.5 -10.5 mg/L, PO₄: 2.6 – 4.5 mg/dL

A) Sodium Disorders

✎ Introduction

- Sodium is the major extracellular cation and is responsible for the majority of the extracellular fluid (ECF) osmolality. Disorders of sodium balance are the most common electrolyte disturbances encountered in clinical practice and occur in both inpatient and ambulatory patients.

✎ Causes

a) Hyponatremia

(1). Hypovolemic hyponatremia

- ✓ Excessive sweating, GI losses, renal losses

(2). Isovolemic hyponatremia

- ✓ SIADH secondary to malignancy, pulmonary disease, CNS disorders, iatrogenic sources

- (3). Hypervolemic hypotonic hyponatremia
 - ✓ Cirrhosis, congestive heart failure

b) Hypernatremia

- (1) Hypovolemic hypernatremia: dermal losses, vomiting, NG suction, lactulose osmotic diuresis—hyperglycemia, mannitol, loop diuretics, concentrated enteral feedings
- (2) Isovolemic hypernatremia: insensible water loss Diabetes insipidus
- (3) Hypervolemic hypernatremia: hypertonic saline

Pathophysiology

- Maintenance of ECF tonicity and Na conc is controlled by homeostatic mechanisms that regulate the intake and excretion of free water.
- Antidiuretic hormone (ADH), also known as *arginine vasopressin*. ADH and the thirst mechanism are efficient at maintaining a normal serum osmolality despite large variations in sodium and water intake.
- While a loss or excess of total body sodium may occur, sodium disorders are primarily caused by abnormalities of water balance.
- Patients with marked hyperglycemia often exhibit hyponatremia. The most often cited correction factor is a decrease in sodium of 1.6 meq/L for every 100 mg/dL increase in glucose concentration.

Sign and Symptoms

- Can range from asymptomatic to life threatening. Symptoms are more apparent when the change in serum sodium is large or develops rapidly.
- Hyponatremia: disorientation, headache, lethargy, malaise, nausea, restlessness, coma, respiratory arrest, seizures
- Hypernatremia: anorexia, weakness, nausea, restlessness, altered mental status, nausea, vomiting, coma, irritability, lethargy.

Treatment of Hyponatremia

- Serum sodium should be corrected at a rate that improves symptoms but does not place the patient at risk for osmotic demyelination.
- In patients with chronic hyponatremia (>48 hours), neurologic complications can be avoided by limiting the correction rate to 10 to 12 mEq/L in 24 hours or 18 mEq/L in 48 hours.
- A correction rate of 2 to 4 mEq/L within 2 to 4 hours may be beneficial in patients with severe symptoms such as seizures
- **Hypovolemic Hypotonic Hyponatremia**
 - ✓ The cornerstone of therapy for hypovolemic hyponatremia is *isotonic (0.9%) saline infusion*. Additionally, specific therapies for underlying causes should be initiated.
- **Isovolemic Hypotonic Hyponatremia**
 - ✓ Fluid restriction is generally considered the cornerstone of therapy for mild or moderate cases of isovolemic hyponatremia.

- ✓ Patients with syndrome of inappropriate diuretic hormone (SIADH) should have fluid restricted to 1 L/d to ensure a negative fluid balance of 500 mL daily.
 - ↳ Medications associated with SIADH should be discontinued.
- ✓ Pharmacologic therapy is reserved for patients not responding to fluid restriction.
 - ↳ Demeclocycline is the preferred agent.
 - ↳ It interferes with the action of ADH in the collecting duct and increases water excretion.
 - Dose: orally in doses of 600 to 1200 mg/d in divided doses.
 - Because of its delayed onset, doses should not be increased for 3 to 4 days

- **Hypervolemic Hypotonic Hyponatremia**

- ✓ The cornerstone of therapy for hyponatremia associated with edema is dietary sodium restriction, water restriction, and diuretic therapy.

- ✍ **Treatment of Hypernatremia**

- Treatment should correct serum sodium at a rate sufficient to alleviate symptoms and not place the patient at risk for cerebral edema.

- **Hypovolemic Hypernatremia**

- ✓ Patients with hemodynamic instability should first receive normal saline until volume status is restored and vital signs are stable. Subsequently, the patient should be switched to hypotonic fluids to correct serum sodium.
- ✓ Oral or enteral replacement with hypotonic fluids is the preferred route. IV is appropriate when oral replacement is not possible.

- **Isovolemic Hypernatremia**

- ✓ Access to free water or replacement with IV hypotonic fluids is the cornerstone of therapy for isovolemic hypernatremia.
- ✓ Patients with central diabetes insipidus require exogenous ADH. Desmopressin is the drug of choice and is typically initiated at a dose of 10 mcg intranasally in the evening.

- **Hypervolemic Hypernatremia**

- ✓ Treatment consists of 5% dextrose infusion with loop diuretics added to promote renal sodium excretion. Since this disorder is commonly iatrogenic and develops within a few hours, rapid correction of serum sodium is safe and appropriate

B) Potassium Disorders

- ✍ **Introduction**

- Potassium is the most plentiful *intracellular cation* in the body. Potassium homeostasis is maintained through intra- and extracellular shifting, predominantly regulated by the *sodium-potassium-adenosine triphosphatase* (Na⁺-K-ATPase) pump.

- Potassium is responsible for many cellular functions, including protein synthesis, cellular metabolism, and conduction of the electrical action potential.

- The normal range for serum potassium concentration is 3.5 to 5.0 mEq/L

Pathophysiology

- Maintenance of the normal range for potassium is affected by diet, acid–base balance, aldosterone, insulin, catecholamines, tonicity of body fluids, and GI and renal excretion.

Hypokalemia

- ✓ Hypokalemia is the finding of a serum potassium concentration less than 3.5 mEq/L and can be classified as **mild** (serum potassium 3–3.5 mEq/L), **moderate** (2.5–3 mEq/L), or **severe** (<2.5 mEq/L). It is caused by a total body deficit of potassium when there is insufficient intake of potassium in the diet or excessive loss through the renal or GI tracts.
- ✓ Hypokalemia caused by the intracellular shift of serum potassium is known as *false hypokalemia* because there is no true deficit in total body content. Hypokalemia is commonly iatrogenic with the most common causes being loop and thiazide diuretics. Hypokalemia may also increase the risk of digoxin toxicity. Increased GI loss of potassium is also a common cause.
- ✓ **Causes:** Poor dietary intake, β -Agonists, loop and thiazide diuretics, theophylline intoxication, caffeine intoxication, insulin overdose, mineralocorticoids, amphotericin B, cisplatin, aminoglycoside

Hyperkalemia

- ✓ Hyperkalemia is defined as a serum potassium concentration >5.5 mEq/L and can be classified as **mild** (5.5–6 mEq/L), **moderate** (6.1–6.9 mEq/L), or **severe** (>7 mEq/L). It is caused by excessive potassium intake in comparison to potassium elimination or when the compartmental distribution of potassium is disrupted.
- ✓ Elevated serum potassium resulting from cellular shifts is known as *false hyperkalemia* since there is no true excess in total body potassium, such as that present in some diabetic ketoacidosis patients upon presentation.
- ✓ Hyperkalemia is commonly associated with acute or chronic kidney disease, especially if patients are noncompliant with dietary restrictions. Potassium disorders are commonly induced by drugs as well as iatrogenic administration of potassium supplements.
- ✓ **Causes:** Dietary noncompliance, spironolactone, amiloride, triamterene, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, trimethoprim, heparin, renal insufficiency, metabolic acidosis (can be falsely high in diabetic ketoacidosis (DKA) as patients often have low total body stores), β -blockers.

✎ Signs and Symptoms

- Hypokalemia: muscle cramps, weakness, malaise, myalgias, impaired muscle function, ECG changes, arrhythmias
- Hyperkalemia: palpitation, ECG changes, arrhythmias, asystole

✎ Treatment of Hypokalemia

• Dietary Potassium

- ✓ Dietary supplementation is recommended for patients with low-normal serum potassium concentrations (3 to 3.5 mEq/L).
- ↳ Nuts, spinach, potatoes, bananas, oranges, meat (beef, pork, lamb)

• Oral Potassium Replacement

- ✓ Oral potassium supplements are preferred whenever possible, especially for asymptomatic patients.
- ✓ It should be given to patients with potassium concentrations of 3 to 3.5 mEq/L who have underlying risk for cardiac arrhythmias.
- ✓ Of the three salt forms available, *chloride* is used more frequently because it is effective for common causes of hypokalemia. *Phosphate* should be reserved for patients with concomitant hypophosphatemia, and *bicarbonate* is advantageous for patients with concurrent metabolic acidosis.

• Intravenous Potassium Replacement

- ✓ IV potassium can be used in patients with severe deficiency, those exhibiting severe symptoms such as electrocardiogram (ECG) changes, or patients unable to tolerate oral supplements.
- ✓ IV therapy is more likely to cause hyperkalemia and may cause damage to the veins and infusion site pain. Typically, 10 to 20 mEq of potassium is diluted in at least 100 mL of 0.9% sodium chloride and administered through a peripheral vein over 1 hour.
- ✓ Patients should be monitored for burning pain and phlebitis at the injection site.

• Alternative therapies

- ✓ Potassium-sparing diuretics such as spironolactone, triamterene, and amiloride are alternatives to chronic exogenous potassium. They may be particularly useful when patients are concomitantly receiving potassium-depleting medication

✎ Treatment of Hyperkalemia

- Along with addressing underlying causes, the treatment options for hyperkalemia consist of dietary restriction, pharmacotherapy, and hemodialysis.
- Asymptomatic patients with *mild hyperkalemia* may be managed with *dietary education* and careful monitoring of potassium concentration. A *loop diuretic* may be added to increase urinary potassium elimination. For patients unable

to tolerate loop diuretics, a cation-exchange resin like sodium polystyrene sulfonate (SPS) may be administered orally or rectally.

- In patients with severe *hyperkalemia* or acute ECG changes, *IV calcium* is administered for stabilization of the cardiac membrane and hemodynamics. *Calcium gluconate* is preferred over *calcium chloride* due to an increased risk of tissue necrosis with the chloride salt if extravasation occurs.
- Concomitantly, an additional therapy should be instituted to *shift potassium intracellularly* and attain a serum potassium concentration less than 5.5 mEq/L. *Sodium bicarbonate*, *insulin with dextrose*, and *albuterol* are available options.

C) Calcium Disorders

✍ Introduction

- Calcium is involved in numerous processes including *propagation of neuromuscular activity*, regulation of the *blood coagulation cascade*, *bone and tooth metabolism*, and *endocrine and exocrine functions*. Under normal conditions, the total serum calcium concentration is **8.5 to 10.5 mg/dL**. Only 0.5% of calcium stores may be found in the ECF, while 99% of calcium stores are found in skeletal bone. ECF calcium is transported in three different forms: bound to plasma proteins, mostly albumin (45%); ionized or free state (40%); and bound to small anions including phosphates, citrates, and bicarbonates (6%). The *unbound or ionized* is the physiologically active form and regulated through complex interactions between PTH, vitamin D, and serum phosphate levels.

✍ Pathophysiology

- The three major hormones that regulate serum calcium and phosphate concentrations are PTH, vitamin D, and calcitonin.
- **PTH** is released from the parathyroid gland in response to a reduction in serum-ionized calcium. Upon release, it acts on the kidneys to *stimulate reabsorption of calcium in the distal tubule* and *increases intestinal absorption of calcium* by increasing renal production of 1-25-dihydroxycholecalciferol (1,25-DHCC or **calcitriol**), the active form of vitamin D. In addition, it stimulates osteoclast and osteoblast activity to *increase calcium mobilization from skeletal bone*. PTH acts in the kidneys to *increase phosphate excretion* by blocking renal reabsorption.
- **Active vitamin D** *increases calcium and phosphate levels by increasing intestinal absorption and renal reabsorption*. Additionally, vitamin D regulates the synthesis and release of PTH.
- **Calcitonin** is released in response to increased ionized calcium concentrations. It increases renal excretion of Ca^{2+} . It also inhibits osteoclasts and stimulates osteoblasts activity, as a result it decreases calcium levels.

✍ Causes:

- **Hypocalcemia:** hypoparathyroidism, vitamin D deficiency, rickets, GI disorders, CKD, hyperphosphatemia, hypoalbuminemia, hypomagnesemia,

loop diuretics, glucocorticoids, calcitonin, phenobarbital, phenytoin, proton pump inhibitors.

- **Hypercalcemia:** malignancy, hyperparathyroidism, thiazide diuretics, lithium, excessive calcium intake, Paget disease, increased thyroid activity, adrenal insufficiency, sarcoidosis

✎ Signs and Symptoms

- **Hypocalcemia:** Paresthesia, muscle cramp, tetany, laryngeal spasm, depression, confusion, memory loss, brittle nails, hair loss, eczema, seizure, MI, arrhythmia, hypotension
- **Hypercalcemia, GI:** nausea, vomiting, abdominal pain, dyspepsia, anorexia, acute pancreatitis; **CNS:** lethargy, obtundation, ataxia, comma; **Cardiac:** ECG changes, arrhythmia, hypertension; **Renal:** polyuria/polydipsia, nephrolithiasis

✎ Treatment

- **Hypocalcemia:**

- ✓ Acute symptomatic hypocalcemia requires IV administration of calcium until signs and symptoms resolve. Administration of 100 to 300 mg of elemental calcium over 10 minutes will usually alleviate symptoms. IV calcium is available in two salt forms: *calcium gluconate* (1 g Ca gluconate = 90 mg elemental calcium) and *calcium chloride* (1 g of Ca chloride = 270 mg elemental calcium). Calcium gluconate administration is preferred over calcium chloride because it is associated with less risk of tissue necrosis
- ✓ Chronic or asymptomatic hypocalcemia due to hypoparathyroidism or vitamin D deficiency may be managed with oral calcium salts or vitamin D replacement. Calcium replacement may begin with 1 to 3 g/d of elemental calcium and progress to a maintenance dose of 2 to 8 g/d in divided doses. Calcium carbonate requires an acidic environment for absorption. Adverse effects of calcium salts include GI upset, constipation, and hypercalcemia.

- **Hypercalcemia**

- ✓ Hypercalcemia treatment involves definitive treatment of primary hyperparathyroidism or malignancy. In patients with drug-induced hypercalcemia, the offending agent should be discontinued. The initial treatment for hypercalcemia in patients without severe renal dysfunction is volume expansion with saline-containing fluids and loop diuretics to enhance urinary excretion of calcium. Loop diuretics block calcium reabsorption in the ascending limb of the loop of Henle. Calcitonin is an alternative treatment that increases renal excretion of calcium by inhibiting bone resorption.
- ✓ Bisphosphonates are first-line treatment in prevention and treatment of malignancy-induced hypercalcemia. They lower calcium levels by inhibiting bone resorption and the formation of osteoclasts.

D) Magnesium Disorders

Overview:

- Magnesium is the second most abundant intracellular cation and is mainly distributed in bone and muscle. The normal range for the serum magnesium concentration is 1.7 to 2.3 mg/dL.
- Magnesium is responsible for many physiologic functions including protein synthesis, function of the cell membrane and mitochondria, and secretion of parathyroid hormone (PTH).
- Serum magnesium concentrations outside the normal range can result in significant alterations in neuromuscular and cardiovascular activity. These changes can have life-threatening consequences including cardiac arrhythmias and paralysis.

Phathophysiology

- Magnesium homeostasis is dependent upon the balance of intake versus output with approximately 30% to 40% of dietary magnesium absorbed in the small bowel. Renal reabsorption of magnesium occurs predominantly in the loop of Henle, with only about 20% of filtered magnesium reabsorbed in the proximal tubule.
- Hypomagnesemia is usually associated with decreased absorption secondary to small bowel disease or increased renal elimination as occurs with diuretic therapy. Hypermagnesemia occurs when magnesium intake is greater than relative elimination by the kidney.

Causes

- Hypomagnesemia: alcoholism, protein malnutrition, malabsorptive disease, vomiting, laxative abuse, diarrhea, bartter syndrome, amphotericin B, aminoglycosides, loop and thiazide diuretics, hyperthyroidism, hypercalcemia, proton pump inhibitors
- Hypermagnesemia: renal insufficiency, treatment of eclampsia, severe preeclampsia, cathartics, lithium therapy, hypothyroidism, Milk-alkali syndrome, Addison disease, DKA

Signs and Symptoms

- Hypomagnesemia: tetany, muscular fasciculation. Convulsions, Trousseau and/or Chvostek sign, palpitations, ECG changes, rrhythmias, hypertension
- Hypermagnesemia: hypotension, flushing, ECG changes, complete heart block, asystole, sedation, coma, hypotonia/hyporeflexia, paralysis, respiratory failure

Treatment

- The treatment of hypomagnesemia can be accomplished by supplementation via oral, IM, or IV routes. The selection of a route of delivery is dependent on the severity of deficiency and associated signs and symptoms. Oral magnesium supplementation can be given to patients with magnesium concentrations more than 1 mEq/L who are asymptomatic. Because IM administration is

painful, it should be limited to patients with limited IV access who warrant more aggressive replacement than can be accomplished with oral supplementation. Patients with severe magnesium deficiency (<1 mEq/L) or signs and symptoms of hypomagnesemia should receive IV repletion until signs and symptoms resolve.

- The treatment of hypermagnesemia is typically addressed in three ways: reduction of intake, enhanced elimination, and antagonism of the adverse effects of elevated magnesium concentrations. IV calcium can be employed to antagonize the neuromuscular and cardiac signs and symptoms of hypermagnesemia. Diuresis to enhance magnesium elimination can be employed in patients without kidney dysfunction. This is usually accomplished via administration of saline accompanied by an IV loop diuretic such as furosemide.

E) Phosphate Disorders

✎ Introduction

- Many of the factors that regulate serum calcium levels also influence serum phosphate levels.
- Phosphate is a major intracellular anion, and normal serum concentrations are **2.6 to 4.5 mg/dL**.
- Phosphate is involved in numerous functions including regulation of enzymatic reactions and metabolism of protein, fats, and carbohydrates. It is a major component of phospholipid membranes of all cells and 2,3 diphosphoglycerate, which regulates the oxygen-carrying capacity of hemoglobin. In addition, it is required for the formation of high-energy bonds in adenosine triphosphate (ATP) production.
- The majority of dietary phosphate is absorbed in the small intestine, and absorption may be increased by 1,25-DHCC. In the kidneys, the elimination of phosphate is dependent on both glomerular filtration and reabsorption in the proximal tubule.

✎ Causes:

- **Hypophosphatemia:** renal tubular dysfunction, increased parathyroid activity, refeeding syndrome, insulin and dextrose treatment for hyperkalemia, alcoholism, malnutrition, phosphate binders, decreased vitamin D intake
- **Hyperphosphatemia:** CKD, tumor lysis syndrome, rhabdomyolysis, septic shock, excessive phosphate administration, increased vitamin D intake.

✎ Signs and Symptoms

- Symptoms of hypophosphatemia may present as the serum phosphate level falls below 2 mg/dL. Most of the symptoms are due to decreased formation of ATP and depletion of 2,3-diphosphoglycerate, which increases the affinity of oxygen for hemoglobin, leading to **tissue hypoxia**. The most common clinical

manifestation of hyperphosphatemia is *hypocalcemia* due to the formation of a calcium-phosphate precipitate, which may lead to *tetany*.

✍ Treatment

- **Hypophosphatemia:** Asymptomatic, mild hypophosphatemia may be treated with oral phosphate. Severe, symptomatic hypophosphatemia should be treated with IV phosphate administration, which are available as a potassium or sodium salt.
- **Hyperphosphatemia:** If tetany is present, IV calcium is required to increase serum calcium levels. The mainstay of pharmacological treatment of hyperphosphatemia is *phosphate binders* administered with each meal and snack to bind dietary phosphate. Oral calcium supplements are considered first-line therapy for long-term treatment. *Calcium carbonate* and *calcium acetate* are two commonly used agents.

3.7. Dosage of Adjustment in Kidney Disease

✍ Dosages of many drugs will require adjustment to prevent toxicity in patients with CKD. Adjustment strategies vary depending on whether the patient is receiving RRT and, if so, the type of RRT. It is suggested that eGFR and in very large or small patients, the eGFR should be multiplied by the actual body surface area to obtain the eGFR in milliliters per minute.

✍ Pharmacokinetic principles guiding therapy adjustments

- **Absorption:** Oral absorption can be decreased in nausea and vomiting, increased gastric pH (uremia), edema, physical binding of drugs to phosphate binders
- **Distribution:** Changes in concentrations in highly water-soluble drugs occur as extracellular fluid status changes. Acidic and neutral protein-bound drugs are displaced by toxin buildup. Other mechanisms include conformational changes of the plasma protein-binding site. Phenytoin is a classic example. The "normal" free fraction of phenytoin is 10%. Free fraction can be as high as 30% in patients with ESRD and hypoalbuminemia.
- **Metabolism:** Variable changes can occur with uremia; metabolites can accumulate.
- **Excretion:** Decreased

✍ Pharmacodynamic changes can also occur (e.g., patients with CKD can be more sensitive to benzodiazepines).

✍ General Recommendations

- 1) Patient history and clinical data
- 2) Estimate CrCl (Jelliffe or Brater equation in AKI; Cockcroft-Gault or MDRD study equations in stable kidney function).
- 3) Identify medications that require modification
- 4) Calculate drug doses individualized for the patient.
✓ Published data

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✍ Pharmacokinetic principles guiding therapy adjustments

- **Absorption:** Oral absorption can be decreased in nausea and vomiting, increased gastric pH (uremia), edema, physical binding of drugs to phosphate binders
- **Distribution:** Changes in concentrations in highly water-soluble drugs occur as extracellular fluid status changes. Acidic and neutral protein-bound drugs are displaced by toxin buildup. Other mechanisms include conformational changes of the plasma protein-binding site. Phenytoin is a classic example. The "normal" free fraction of phenytoin is 10%. Free fraction can be as high as 30% in patients with ESRD and hypoalbuminemia.
- **Metabolism:** Variable changes can occur with uremia; metabolites can accumulate.
- **Excretion:** Decreased

✍ Pharmacodynamic changes can also occur (e.g., patients with CKD can be more sensitive to benzodiazepines).

✍ General Recommendations

- 1) Patient history and clinical data
- 2) Estimate CrCl (Jelliffe or Brater equation in AKI; Cockcroft-Gault or MDRD study equations in stable kidney function).
- 3) Identify medications that require modification
- 4) Calculate drug doses individualized for the patient.
✓ Published data

- ✓ Rowland-Tozer estimate: $Q = 1 - [Fe (1 - KF)]$
 - ❖ Q = kinetic parameter or drug dose adjustment factor
 - ❖ Fe = fraction of drug excreted unchanged in the urine
 - ❖ KF = ratio of patient's CrCl to normal (120 mL/minute/1.73 m²)
- 5) Monitor patient (e.g., kidney function, clinical parameters) and drug concentration (if applicable).
- 6) Revise regimen as appropriate.

Table 3.2 Dose adjustments and precautions in decreased kidney function¹

Drug Class	Agents Requiring Dose Adjustment
Antibiotics	Almost all antibiotics require dosage adjustment (exceptions: ceftriaxone, clindamycin, linezolid, metronidazole, macrolides, nafcillin)
Anticoagulants	Enoxaparin, fondaparinux, apixaban, rivaroxaban, edoxaban, dabigatran
Cardiac medications	Atenolol, ACEIs, digoxin, nadolol, sotalol; avoid potassium-sparing diuretics if CrCl < 30 mL/min/1.73 m ²
Lipid-lowering therapy	Clofibrate, fenofibrate, statins (particularly rosuvastatin)
Narcotics	Codeine, avoid meperidine; other agents may also accumulate
Antipsychotic and antiepileptic agents	Gabapentin, lacosamide, levetiracetam, lithium, paroxetine, primidone, topiramate, trazodone, vigabatrin
Hypoglycemic agents	Acarbose, alogliptin, canagliflozin, chlorpropamide, dapagliflozin, exenatide, glyburide, glipizide, insulins, liraglutide, metformin, saxagliptin, sitagliptin
Antiretrovirals	Individualize therapy: Monitor CD4+ counts, viral load, and adverse effects (agents requiring dose adjustment: lamivudine, adefovir, emtricitabine, stavudine, tenofovir, and zidovudine)

Drug Dosing in HD

- Dosing changes in patients with HD may be necessary because of accumulation caused by kidney failure or because the procedure may remove the drug from the circulation or because of pharmacodynamic effects (e.g., blood pressure medication reduction because of intradialytic hypotension).

1) Drug-related factors affecting drug removal during dialysis:

- ✓ Molecular weight: With high-flux membranes, larger molecules (e.g., vancomycin) can be removed than with conventional filters.
- ✓ Water soluble: Insoluble drugs are unlikely to be removed.
- ✓ Protein binding: Because albumin cannot pass through membranes, protein-bound drugs cannot either.

¹ Bondi DS, Bridgeman MM, Burke JM, et al. **Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course**, 2021 ed. Lenexa, KS: American College of Clinical Pharmacy, 2021